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BREVET SPÉCIAL DE MÉDICAMENT

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Classification internationale : A 61 *k* — C 07 *d*

Le nicotinate de cétyle comme antalgique et révulsif et les compositions pharmaceutiques pour son administration, notamment par voie percutanée.

Société civile dite : SOCIÉTÉ D'ÉTUDES ET DE RECHERCHES PHARMACOTECHNIQUES
résidant dans la Principauté de Monaco.

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Délivré par arrêté du 22 avril 1963.

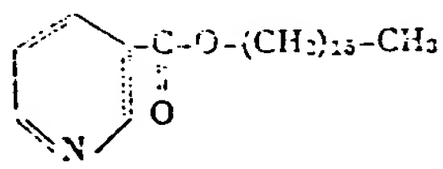
(*Bulletin officiel de la Propriété industrielle [B.S.M.]*, n° 21 de 1963.)

La présente invention est relative à la thérapeutique antalgique et révulsive par application locale d'un ester de l'acide nicotinique. Elle vise plus particulièrement l'utilisation en thérapeutique humaine d'un nouveau nicotinate d'alcool gras à longue chaîne et les compositions pharmaceutiques préparées en vue d'une telle utilisation.

La nouvelle composition pharmaceutique formant l'objet du médicament conforme à l'invention se distingue notamment par le fait qu'elle contient une quantité thérapeutiquement active de nicotinate de cétyle.

Cette substance active n'a pas encore été décrite dans la littérature et constitue en elle-même un produit industriel nouveau dont aucune utilisation, thérapeutique ou autre, n'a évidemment encore été décrite.

Elle correspond à la formule développée ci-dessous :



La formule brute peut donc s'écrire C_{22} H_{37} NO_2, le poids moléculaire étant de 347.

Les esters nicotiniques connus (tels que, par exemple, le nicotinate de méthyle) présentent des propriétés révulsives hyperémiantes par vaso-dilatation locale. Ils sont actuellement utilisés sous forme de compositions à usage externe (liniments, baumes, pommades, onguents, etc.).

On sait toutefois que l'action exercée par ces esters d'alcools gras inférieurs est relativement brutale et fugace.

Dans le cadre de l'invention, on a pensé modifier l'activité en estérifiant l'acide nicotinique, non plus par un alcool gras inférieur, mais par un alcool grad lourd, notamment l'alcool cétylique, en vue de tempérer l'action révulsive et de la rendre plus durable et plus diffée.

Le nicotinate de cétyle est donc un composé original à un double point de vue :

Originalité chimique, car il n'a pas encore été décrit.

Originalité pharmacologique et clinique, son action étant, parmi les produits de ce type, la mieux adaptée à l'application cutanée.

On peut notamment préparer le nicotinate de cétyle, qui constitue la substance active du nouveau médicament conforme à l'invention, par réaction de quantités sensiblement équimoléculaires d'alcool cétylique et de chlorhydrate de chlorure de nicotinoyle, en opérant de préférence au sein d'un solvant organique inerte et anhydre tel que le benzène. Par traitement du chlorhydrate ainsi obtenu par de l'ammoniaque diluée, on libère ensuite l'ester pyridinecarboxylique désiré.

On peut opérer de la manière suivante :

Dans un ballon bien sec de 2 litres à 3 tubulures, muni d'un agitateur, d'une ampoule à brome, d'un réfrigérant ascendant et d'un thermomètre, on introduit 173 g de chlorhydrate de chlorure de nicotinoyle fraîchement préparé, 150 ml de benzène anhydre et, peu à peu, par l'ampoule à brome, 242 g d'alcool cétylique préalablement dissous dans 250 ml de benzène anhydre.

On parachève la réaction en chauffant le mélange au bain-marie pendant une heure et demie.

On laisse refroidir, puis on verse la suspension benzénique de chlorhydrate de l'ester dans un mélange de 500 ml d'eau et de 250 g de glace pilée; on ajuste à pH6-6,5 par de l'ammoniaque à 20 % (environ 100 ml).

L'ester libéré passe en solution dans le benzène. On réunit les phases benzéniques et l'on filtre sur noir animal. On sèche sur sulfate de sodium anhydre et l'on concentre sous pression réduite en veillant

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à ce que la température de la masse reste inférieure à 95 °C.

Par refroidissement, l'ester cristallise.

On obtient 180 g de produit. Si on le désire, on peut le purifier par recristallisation.

Le produit obtenu est une poudre blanche onctueuse, insoluble dans l'eau, soluble dans l'alcool et le benzène et fondant à 45°-47 °C (bloc Maquenne).

Conformément à l'invention, on a pu reconnaître par des essais pharmacologiques que cette nouvelle substance est douée de propriétés thérapeutiques intéressantes et qu'elle manifeste notamment, en applications locales, une activité révulsive et hyperémiante par dilatation des capillaires et petits vaisseaux.

D'autre part, sa toxicité est faible et on n'a constaté aucun phénomène d'irritation locale ni aucune manifestation d'intolérance en administration percutanée.

L'action vaso-dilatatrice a pu être mise en évidence par pléthysmographie de la patte de chien ou, plus facilement encore, par observation de l'érythrodermie apparue chez l'animal après application locale d'une pommade dosée à 1 % de substance active. Cette action relativement douce persiste pendant quelque temps.

Les essais cliniques effectués ont permis d'obtenir des résultats intéressants dans le traitement d'algies diverses, articulaires ou musculaires, de lumbagos, de torticolis.

On a obtenu également de nettes améliorations dans les troubles de la circulation périphérique : engelures, acrocyanoses, refroidissement des extrémités.

On a appliqué 2 à 5 fois par jour une composition renfermant 1 % de principe actif.

Dans des cas de myalgies, l'application en massages a provoqué une nette diminution de la douleur et une sensation de chaleur au niveau de la zone douloureuse.

Le médicament conforme à l'invention peut être avantageusement présenté sous forme d'une pommade préparée au moyen de tout excipient usuel et dosée à un taux compris entre 1 et 5 % de nicotinate de cétyle, administrable en frictions ou massages. On peut le présenter également sous forme de liniment, lotion, embrocation, crème émulsionnée ou anhydre.

Conformément à un mode de réalisation préférentiel de l'invention, on peut associer au nicotinate de cétyle d'autres produits destinés à en compléter l'action, par exemple, des dérivés salicylés connus pour leurs propriétés anti-rhumatismales.

On indique ci-après, à titre d'exemples non limitatifs, quelques compositions pharmaceutiques conformes à l'invention.

Exemple 1 (crème émulsionnée) :

Nicotinate de cétyle	1 g
Monostéarate de propylèneglycol	19,5 g
Huile de vaseline	1,5 g
Vaseline	3 g
p-Hydroxybenzoate de méthyle	0,5 g
Eau	100 g

Exemple 2 (crème émulsionnée) :

Nicotinate de cétyle	1,5 g
Stéarate de diéthylèneglycol	20 g
Huile de paraffine	3 g
Huile de palme hydrogénée interestérifiée	5 g
Vaseline	5 g
p-Hydroxybenzoate de méthyle	0,1 g
Eau	100 g

Exemple 3 (crème anhydre) :

Nicotinate de cétyle	2 g
Salicylate de diéthylamine	5 g
Polyéthylèneglycol (PM 1 500)	q.s.p. 100 g

Bien entendu, l'invention n'est nullement limitée aux divers modes de réalisation ci-dessus décrits, qui ne l'ont été qu'à titre d'exemples.

RÉSUMÉ

L'invention a pour objet, à titre de médicament nouveau et principalement utile pour le traitement percutané des algies musculaires et articulaires et des troubles de la circulation périphérique, une composition pharmaceutique remarquable notamment par les caractéristiques suivantes, considérées séparément ou en combinaison :

1° Elle contient une quantité thérapeutiquement active de nicotinate de cétyle;

2° Conformément à un mode de réalisation préférentiel, elle est présentée sous forme d'une crème à 1 à 2 % de substance active;

3° La composition est destinée au traitement des affections rhumatismales et contient un agent connu pour le traitement de telles affections, par exemple un dérivé salicylique.

Société civile dite :
SOCIÉTÉ D'ÉTUDES ET DE RECHERCHES PHARMACOTECHNIQUES

Par procuration :
G. MASSON

AVIS DOCUMENTAIRE SUR LA NOUVEAUTÉ

Documents susceptibles de porter atteinte à la nouveauté du médicament : *néant.*

Documents illustrant l'état de la technique en la matière :

— *Journal of American Chemical Society*, vol. 67, *CO. BADGETT et alii*, pages 1135-1138 (1945);

— *Bull. Soc. Chimique de France, R. CHARONNAT et coll.*, pages 1014-1017 (1948).

Pour la vente des fascicules, s'adresser à l'IMPRIMERIE NATIONALE, 27, rue de la Convention, Paris (15e).

PATENT SPECIFICATION

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International Classification:—C07c.

COMPLETE SPECIFICATION

Preparation of α-β,δ-ε-unsaturated Carboxylic Derivatives

We, MONTECATINI SOCIETA GENERALE PER L'INDUSTRIA MINERARIA E CHIMICA, a body corporate organised and existing under the laws of Italy, of 1—2, Largo Guicho Donegari, Turati, Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to α-β,δ-ε-unsaturated carboxylic derivatives and to their preparation.

It is known that allyl chloro-derivatives, by treatment with nickel carbonyl under atmospheric pressure, can yield addition products. (J. W. Copenhaver—Acetylene and Carbon Monoxide Chemistry, New York 1949).

It is also known that acetylene, by treatment with nickel carbonyl in the presence of water and/or alcohols, yields acrylic acid and acrylic esters. (J. D. Webb and G. I. Borcherdt J.A.C.S. 1951, 2654 and B.A. 2524, 833 1950).

We have now found that, if acetylene and a chloro-derivative of the allyl type are reacted with nickel-carbonyl in the presence of hydroxylic solvents (R^1OH), a product is obtained resulting from the linear combination of R^1OH, carbon monoxide, acetylene and the chloro-derivative.

The process allows carboxylic derivatives containing 3 carbon atoms more than the starting chloro-derivatives to be obtained.

The invention provides α-β,δ-ε-unsaturated carboxylic derivatives having the general formula:—

$$R—[(CH_2)_n^1—CH=CH—CH_2—CH=CH—COOR^1]_n$$

where n is 1 or 2,

n^1 is 0 or 1.

R is H or an aliphatic group containing up to 20 carbon atoms with or without substituent groups, and

R^1 is H or an aliphatic, hydroxyaliphatic or arylaliphatic or cycloaliphatic group containing not more than 20 carbon atoms; except 2,5-heptadienoic and 2,5-octadienoic acids in which the double bond conjugated with the carboxyl group is in the trans-configuration.

Morton *et al* have described a hepta-2,5-dienoic acid and an octa-2,5-dienoic acid in J.A.C.S. (1950) 72 on page 3790. These acids have the double bond conjugated with the carboxyl group in the trans-configuration and melt at higher temperatures than the corresponding acids of the invention.

Compounds included in the invention are:—

2,5-hexadienoic acid,
methyl ester of 2,5-hexadienoic acid,
ethyl ester of 2,5-hexadienoic acid,
isopropylester of 2,5-hexadienoic acid,
benzyl ester of 2,5-hexadienoic acid,
ethylene glycol esters of 2,5-hexadienoic acid, 2,5-heptadienoic acid, in which the double bond which is conjugated with the carboxyl group is in the cis-configuration
methyl ester of 2,5-heptadienoic acid,
methyl 7-acetoxy-2,5-heptadienoate,
7-cyano-2,5-heptadienoic acid,
methyl ester of 7-cyano-2,5-heptadienoic acid,
isopropyl ester of 7-cyano-2,5-heptadienoic acid,
cyclohexyl ester of 7-cyano-2,5-heptadienoic acid,

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dimethyl ester of 2,5-octadiendioic acid,
and
dimethyl tetradeca-2,5,9,12-tetraendioate.

According to the invention these compounds may be prepared by a process which comprises a method for the preparation of α-β,δ-ε-unsaturated carboxylic derivatives having the general formula defined above, which comprises reacting an allyl derivative of the general formula

$$R—[(CH_2)_{n^1}—CH=CH—CH_2Cl]_n,$$

wherein R, n^1 and n are as defined above, and acetylene with solution of nickel carbonyl in a solvent having the general formula R^1OH wherein R^1 is as defined above.

By the method of the invention, it is possible to synthesise a wide variety of unsaturated carboxylic compounds in a surprisingly easy way, since the process is carried out at room temperature or at a not very different temperature under atmospheric pressure, and the desired product is obtained in a single stage.

In this way a considerable number of carboxylic acids and esters thereof become easily accessible, either in the unsaturated or in the saturated form the latter being easily obtainable from the first one by conventional hydrogenation methods.

Both the unsaturated and saturated compounds have several possible uses, for instance, in the plasticizer and solvent fields and as intermediates for the synthesis of other organic products.

This synthesis also presents further advantages since, as starting materials, chloro-derivatives can be used containing other substituent groups such as carboxyl or hydroxyl groups which make it possible to obtain polyfunctional or substituted unsaturated acids.

The synthesis can schematically and briefly be represented by the following equation:—

$$R\text{-}(CH{=}CH{-}CH_2Cl)_n + [CO + C_2H_2 + R'OH]_n \xrightarrow{Ni(CO)_4} R\text{-}(CH_2{-}CH{=}CH{-}CH_2{-}CH{=}CH{-}COOR')_n + (HCl)_n$$

The synthesis takes place in general at temperatures of between 0° and 75° C. in the presence of acetylene and carbon monoxide. The temperature range for the practical execution of the reaction depends on the reactivity of the allyl derivatives and alcohols used and is in general comprised between 25° and 60° C.

The carbon monoxide needed for the synthesis is supplied by the nickel carbonyl and further CO gas may be introduced together with acetylene into the reaction zone.

The true synthesis, in fact, does not require the use of the stoichiometric amount of nickel carbonyl to form nickel chloride from the starting chloro-derivative but only the renewal of the amount of nickel carbonyl which is lost in other ways.

The following scheme approximatively represents the action of the nickel carbonyl in the synthesis:—

$$R{-}CH{=}CH{-}CH_2Cl + C_2H_2 + Ni(CO)_4 \rightarrow \left[\begin{matrix} CO & CO \\ & Ni \\ CO & \end{matrix} \; CO{-}CH{=}CH{-}CH_2{-}CH{=}CH{-}R\right]^+ Cl^- \xrightarrow[CO]{R'OH} Ni(CO)_4 + R'OOC{-}CH{=}CH{-}CH_2{-}CH{=}CH{-}R + HCl$$

The chlorine of these derivatives reacts easily with nickel carbonyl to give addition products of the organic radical bound to the chlorine atom and nickel chloride. The nickel

carbonyl consumption can therefore vary according to the ease of side reactions of the chloro-derivative and therefore also the amount of carbon monoxide to be supplied as a gas is variable.

Another cause of side reactions is the presence of hydrochloric acid whose action however can be eliminated by using either buffers ($MgCO_3$, $CACO_3$, NaH_2PO4), or inert solvents, such as acetone, glycol ethers or diethylketone.

The use of solvents also serves to facilitate the formation of a homogeneous phase when this is necessary due to the difficulty of dissolving the reactants.

The reactant alcohols can be used in a large excess in order to obtain good solubility as well as dilution of free hydrochloric acid, whereby saponification during the reaction, can be avoided. This precaution is particularly necessary when operating at temperatures well above room temperature. In the presence of water it is convenient to dilute with inert solvents, such as acetone. When mixtures of water and alcohols are used, esters are prevailingly formed if the water proportion is not high. An excess of the hydroxyl compound in respect of the stoichiometric amount is advantageous for the execution of the synthesis and for the yield of the useful product. Also an excess of acetylene in respect of the chlorine of the reacting allyl derivative is useful and it should preferably be higher than 20%; one must however take into account the fact that, in the presence of hydrochloric acid and acetylene, the latter being in excess with respect to the allyl derivative and CO, the reaction which leads to the formation of acrylic acid and acrylic esters is promoted. In order to limit this reaction, it is useful to operate with a gaseous mixture containing a sufficient amount of CO. By operating without CO in the gaseous mixture, higher amounts of acrylic acid or esters thereof and of other by-products are formed while increasing the nickel carbonyl consumption.

Nickel carbonyl must also be present in the reaction zone, preferably in excess of the reacting chloro-derivative. When operating with a gas current, the excess of nickel carbonyl in respect of the amount required for the reaction, is substantially removed by the gases which, if desired, can be recycled.

At the end of the reaction, nickel carbonyl is found in the form of nickel chloride.

The preparation of the allyl derivatives may be carried out by various methods, mainly by direct chlorination of olefins, such as allyl chloride from propyiene and chlorine; by addition of hydrochloric acid to dienes such as, in the case of crotyl chloride, from butadiene and hydrochloric acid; by chlorination of unsaturated alcohols with PCl_3 or HCl such as in the case of chloroacetoxybutene from acetoxy butenol; further by dehydrochlorination of dichloro-derivatives or dehydration of chloro-alcohols.

The rate of addition of the reactants should conveniently be controlled in such a way as to avoid a green colour, so as to avoid excessive nickel carbonyl consumption. The heat of reaction, besides being controlled by gradual addition of the reactants, can also be controlled by the conventional cooling systems.

The low temperature causes the secondary reaction to decrease. The reaction time depends on the temperature and on the particular nature of the allyl derivative used.

By operating continuously with recycling of gas, there is the advantage of introducing nickel carbonyl amounts only slightly higher than those actually consumed during the reaction thus reducing the losses.

Also it is possible to carefully control the reaction conditions by keeping constant the composition of the circulating gaseous mixture and introducing fresh gas in the cycle, according to the reaction requirements. Accordingly an increase in the yield and a decrease in the nickel carbonyl consumption occur.

In the case of chlorocyano-butene it is preferable to keep the concentration of acetylene in the gas at between 55 and 75% and that of carbon monoxide at between 24 and 45%. An effective gas circulation favours the mixing and has a favourable influence on the reaction course.

The slow and regular introduction of the reactants in diluted solution favours the reaction and allows the best results to be obtained.

Diluted solutions are preferably used so that, in total, more than 10 parts solvent are introduced per 1 part allyl derivative.

At the end of the reaction it is convenient to distill off first the alcohol and the solvent and then the product either directly or after having added water and separated the nickel chloride solution. In the case where acids are produced, they can be isolated as alkali metal salts and then freed by acidification.

The residual nickel chloride solution allows the nickel to be easily recovered as carbonyl, by using the known method already employed for recovering nickel in the synthesis of acrylic esters from acetylene. In fact, by transforming it into nickel hydroxide or into an ammonium complex and subjecting the suspension or solution thus obtained to the action of carbon monoxide under pressure, nickel carbonyl can be obtained without any difficulty.

The products obtained, are characterised in that they contain carbon atom groupings which contain two non-conjugated double bonds, one of which is conjugated with the carboxylic group. They are rather stable products in which the double bond conjugated with the carboxylic group is prevailingly in the *cis*-

form. By heating to about 250° C., transformation into the *trans*-form in general takes place quickly together with side reactions. The products can easily be hydrogenated by known methods. Saturated derivatives, many of which having a wide use, are thus obtained.

Some of the compounds obtained by this synthesis deserve to be mentioned due to their practical importance and the cheapness of the raw materials used. Particularly interesting are 7-cyano-2,5-heptadienoic acid and its esters, which are obtained from 1-chloro-4-cyano-butene-2.

7-cyano-2,5-heptadienoic acid was separated as a viscous oil. The methyl ester of this acid distills at 134—138° C./7 mm Hg, n_D^{20} 1.4788. The isopropyl ester distills at 160—165°/13 mm Hg. The cyclohexyl ester distills at 180—183/5 mm Hg.

2,5-hexadienoic acid, $CH_2=CH—CH_2—CH=CH—COOH$ was isolated as a liquid having a boiling point of 95—105° C/12 mm Hg. Caproic acid is obtained by hydrogenation of this acid.

The methyl ester of 2,5-hexadienoic acid boils at 63—66° C/34 mm Hg, n_D^{20} 1.4495; its ethyl ester boils at between 50 and 55° C/10 mm Hg, its isopropyl ester at 36—42° C/5 mm Hg and its benzyl ester at 150—165° C/20 mm Hg.

From crotyl chloride, obtainable from butadiene and hydrochloric acid, 2,5-heptadienoic acid $CH_3—CH=CH—CH_2—CH=CH—COOH$ was obtained as a liquid boiling at 117—124° C/15 mm Hg. By hydrogenation, heptanoic acid is obtained.

The methyl ester of this acid boils at about 72—75° C/20 mm Hg, $n_D^{20}=1.4567$.

From chloroacetoxybutene, obtainable from 1,4-dichlorobutene-2 and sodium acetate, the methyl ester of 7-acetoxy-2,5-heptadienoic acid was obtained, a liquid boiling at 122—129° C/6 mm Hg having the following formula:—

$$CH_3COO—CH_2CH=CH—CH_2—CH=CH—COOCH_3$$

From the methyl ester of 5-chloro-3-pentenoic acid was obtained the dimethyl diester of 2,5-octadiendioic acid, a liquid with a boiling point of 133—138° C/8 mm Hg, having the formula:—

$$H_3C—OOC—CH=CH—CH_2—CH=CH—COOCH_3$$

By hydrogenation of this ester, dimethyl suberate is obtained.

From 1,8-dichloro-2,6-octadiene, obtained by chlorination of the dimerization product of chloroacetoxy butene, dimethyl tetradeca-2,5,9,12-tetraendioate, isolated as a liquid boiling at about 200—210°/10 mm Hg, is obtained:—

$$H_3C—OOC—CH=CH—CH_2—CH=CH—CH_2—CH_2—CH=CH—CH_2—CH=CH—COOCH_3$$

By hydrogenation on Pd in methanol, the diethyl tetradecandioate is obtained, a known product which crystallizes during the hydrogenation and has a melting point of 41° C.

Some illustrative examples are set out below

EXAMPLE 1.

Into a 500 cc flask containing 200 cc methyl alcohol and provided with stirrer, reflux condenser, thermometer, gas inlet pipe and two separatory funnels joined in a single stem dipping in the liquid, acetylene at a rate of 10 l. per hour is introduced at 45° C, after washing the flask with nitrogen; meanwhile two 100 cc methanol solutions containing 30 g nickel carbonyl and 40 g chlorocyanobutene, respectively are dropped into the flask.

After a 4 hour reaction, the whole is cooled and the alcohol is distilled off together with a little methyl acrylate. The residue is mixed with water, the double layer is separated, dried on sodium sulphate and distilled thus collecting 25 g of the fraction distilling at 140—150° C under 13 mm Hg, which contains the methyl ester of 7-cyano-2,5-heptadienoic acid.

From the nickel content of the aqueous solution is appears that 25 g nickel carbonyl have reacted.

Analysis of the distillate:

Found	C 64.91%	H 6.87	N 8.06
Calculated for $C_9H_{11}NO_2$	C 65.44%	H 6.71	N 8.48

EXAMPLE 2.

Into a 500 cc flask provided with stirrer, reflux condenser, thermometer, gas inlet pipe and two separatory funnels joined in a single stem, a mixture of 10 litre/h acetylene and 10 litre/h carbon monoxide is introduced at 45° C (after washing with nitrogen). The gas is bubbled through a pipe immersed in 200 cc methanol.

Through both funnels equal volumes of two solutions containing respectively 50 g nickel carbonyl and 40 g chlorocyanobutene in 100 cc methanol are dropped into the flask over 3 hours; 13g nickel carbonyl come out with the gas. Introduction of gases is continued until the solution assumes a greenish colour. It is then cooled, nitrogen is introduced and methyl alcohol and a little nickel carbonyl are distilled off. The residue is mixed with water and a double layer is separated. After drying on sodium sulphate and distilling at 140—160° C/13 mm Hg, 40 g

methyl ester of 7-cyano-2,5-heptadienoic acid consisting of a liquid which becomes yellow quickly, are obtained.

From the nickel content of the aqueous solution it appears that 15 g nickel carbonyl have been decomposed.

EXAMPLE 3.

Into a 1000 cc flask provided with stirrer, reflux condenser, thermometer, gas inlet pipe and two separatory funnels joined in a single stem, a mixture of 10 litre/h acetylene and 10 litre/h carbon monoxide is introduced at 35° C. (after washing with nitrogen). The gas is bubbled through 400 cc methanol. Equal volumes of two methanol solutions containing in 100 cc respectively 30 g nickel carbonyl and 40 g chlorocyanobutene are dropped into the flask over 6 hours. Operating as in the preceding example, a fraction weighing 45 g and containing the methyl ester of 7-cyano-2,5-heptadienoic acid is distilled off at between 140 and 160° C. under 13 mm Hg.

From the nickel content of the aqueous solution it appears that 6 g nickel carbonyl have been decomposed.

EXAMPLE 4.

Into a flask equipped with stirrer, reflux condenser, thermometer, gas inlet pipe and separatory funnels, 100 cc acetone and 10 cc water are introduced. The temperature is raised to 40° C. and a stream of 6 litre/h acetylene and 6 litre/h carbon monoxide is introduced. Simultaneously 20 g chlorocyanobutene and 11 cc nickel carbonyl are introduced over about 3 hours. The solution becomes brown and nickel chloride is separated.

Acetone is distilled off, the residue is mixed with water and the oil thus formed is separated; 13 g 7-cyano-2,5-heptadienoic acid are extracted with sodium bicarbonate and then freed by treatment with sulphuric acid.

EXAMPLE 5.

Into a 500 cc flask identical with that described in the preceding examples a mixture of 20 g chlorocyanobutene and 15 g nickel carbonyl in isopropyl alcohol is reacted at 45° C. while a current of 4 litre/h CO and 6 litre/h acetylene is introduced at the same time.

After 4 hours reaction isopropyl alcohol is distilled off, under a slight vacuum, the residue is mixed with water, the oily layer is separated and distilled under a vacuum of 13 mm Hg. At 160—165° C 20 g of a clear liquid consisting of the isopropyl ester of 7-cyano-2,5-heptadienoic acid are collected.

Analysis:—

Found	C 68.17	H 8.01	N 7.84
Calculated for $C_{11}H_{15}NO_2$	C 68.37	H 7.82	N 7.25

EXAMPLE 6.

50 cc cyclohexanol are reacted at 45° C, under a stream of CO and acetylene, with 10 g chlorocyanobutene and 6 cc nickel carbonyl for 4 hours.

The product is distilled under vacuum in order to remove cyclohexanol, mixed with water, extracted with ether and distilled under a vacuum of 5 mm Hg.

At 180—183° C, 7 g cyclohexyl ester of 7-cyano-2,5-heptadienoic acid, a viscous liquid containing dicyanoctadiene as an impurity, are collected.

Analysis:—

Found	C 70.78	H 8.03	N 6.82
Calculated for $C_{14}H_{19}NO_2$	C 72.07	H 8.21	N 6.00

EXAMPLE 7.

Into a flask kept at 35° C by means of a water bath, 250 cc acetone and 20 cc water are introduced. The mixture is kept under agitation by a mechanical stirrer. Air is removed by means of an oxygen-free nitrogen stream and a gas stream consisting of 10 l/h CO and 10 l/h C_2H_2 is then introduced. Two acetone solutions containing 25 g allyl chloride and 30 g nickel carbonyl respectively are then added dropwise. The solution gradually assumes a brown-yellow colour. The addition of the reactants requires 6 hours.

From the solution, nickel chloride crystals are separated. The mixture is kept at the above temperature for 1 hour, nitrogen is then introduced again and the volatile compounds are distilled under a slight vacuum. The residue is mixed with water and extracted with ether.

The residual solution contains 3.9 g nickel chloride, corresponding to 11.3 g nickel carbonyl consumed.

By distilling the residue of the ether extract under a suction of 12 mm Hg, 17 g 2,5-hexadienoic acid are recovered at between 95 and 105° C. (Acidimetric equivalent 114).

Caproic acid is obtained by hydrogenating this acid on Pd at room temperature.

EXAMPLE 8.

Into a flask, provided with a mechanical stirrer and reflux condenser, containing 400 cc methyl alcohol, kept at 35° C and through which a stream of 10 l/h CO and 10 l/h C_2H_2 is passed, 25 g allyl chloride and 30 g nickel carbonyl are added dropwise together over 6 hours.

The solution assumes first a yellow and then a brown-red colour. During the change in colour the temperature rises and it is necessary to cool and to add gradually the reac-

tants in order to control the heat of reaction.

After 1 hour it is washed with nitrogen and the volatile portion, which boils up to 80° C. under atmospheric pressure, is distilled under a slight vacuum.

The residue is mixed with water. The nickel content of the aqueous solution amounts to 7.7 g, corresponding to a nickel carbonyl consumption of 21 g.

The product is mixed with ether, is dried on sodium sulphate and filtered, the ether is removed and the product is distilled. Under a vacuum of 12 mm Hg, at between 35 and 40° C. a fraction of 16 g containing methyl 2,5-hexadienoate is obtained.

This ester, by hydrogenation on Pd at room temperature, yields methyl caproate.

EXAMPLE 9.

Into a flask containing 300 cc ethyl alcohol, through which 10 l/h CO and 10 l/h C_2H_2 are passed, 25 g allyl chloride and 30 g nickel carbonyl in an ethanol solution are added, at 45° C. within 3 hours.

Operating as in the preceding example, 14 g of a fraction having a boiling point of 50—55° C/10 mm Hg and containing the ethyl ester of 2,5-hexadienoic acid, are obtained and 18 g nickel carbonyl are consumed.

EXAMPLE 10.

Into a flask containing 400 cc isopropyl alcohol, through which 10 l/h CO and 10 l/h C_2H_2 are passed, two solutions of 25 g allyl chloride and 30 g nickel carbonyl in 100 cc isopropyl alcohol are added at 40° C over 4 hours.

Operating as in the preceding example, 16 g of isopropyl ester of 2,5-hexadienoic acid, having a boiling point of 36—42° C/5 mm Hg, are obtained and 22 g nickel carbonyl are consumed.

EXAMPLE 11.

Into a flask containing 130 g benzyl alcohol and 250 cc acetone in which 10 l/h CO and 10 l/h C_2H_2 are introduced, 25 g allyl chloride and 30 g nickel carbonyl in acetone solution are added at 40° C. within 4 hours.

Operating as in the preceding example, 20 g of a fraction having a boiling point of 150—162° C/20 mm Hg, and containing the benzyl ester of 2,5-hexadienoic acid, are obtained. 17 g nickel carbonyl are consumed.

EXAMPLE 12.

Into a flask containing 100 cc ethylene glycol and 300 cc acetone, two acetone solutions of 25 g allyl chloride and 30 g nickel carbonyl are added at 40° C over 4 hours under a stream of 10 l/h CO and C_2H_2.

From the solution, nickel chloride crystals are separated. Operating as in the preceding example but after having washed the ether extract with water in order to remove ethylene glycol, 23 g of glycol esters of 2,5-hexadienoic acid, mainly glycol monoester of 2,5-hexadienoic acid, are distilled at between 80 and 120° C under 8 mm Hg.

EXAMPLE 13.

Two acetone solutions of 25 g crotyl chloride and 25 g nickel carbonyl are reacted by introducing them at 30° C into a flask containing 300 cc acetone and 30 g water while 10 l/h CO and 10 l/h C_2H_2 are passed through for 6 hours.

Nickel chloride crystals are separated from the solution. The products are separated by operating as in Example 7.

Under a vacuum of 15 mm Hg, 19 g of a fraction having a boiling point of 117—124° C containing 2,5-heptadienoic acid, are distilled (Acidimetric equivalent 125).

14.8 g nickel carbonyl are consumed.

Heptadienoic acid, by hydrogenation on Pd at room temperature, yields heptanoic acid.

EXAMPLE 14.

25 g crotyl chloride and 25 g nickel carbonyl are introduced at 30° over 6 hours into a flask, as in the preceding examples, containing 400 cc methyl alcohol, while a stream of 10 l/h CO and 10 l/h C_2H_2 are passed through the same flask.

Operating as in Example 8, 28 g of a raw product are obtained which, by distillation under a vacuum of 10 mm Hg, yields 20 g. 2,5-heptadienoic acid methyl ester at 58—62° C.

14.5 g nickel carbonyl are consumed.

Methyl heptadienoate, by hydrogenation on Pd at room temperature, yields methyl heptanoate.

EXAMPLE 15.

18 g methyl ester of 5-chloro-3-pentenoic acid and 10 g nickel carbonyl are reacted at 30° C for 6 hours in the presence of 5 g $MgCO_3$ and 400 cc methyl alcohol under a stream of 5 l/h CO and 5 l/h C_2H_2. 2.7 g nickel carbonyl are consumed. By vacuum distillation 13 g are obtained, distilling at 133—138° C/8 mm Hg and consisting of dimethyl diester of 2,5-octadiendioic acid.

This ester by hydrogenation on Pd yields dimethyl suberate.

EXAMPLE 16.

30 g 1-chloro-4-acetoxy butene-2 in methyl alcohol and 20 g nickel carbonyl in methyl alcohol are introduced while stirring into a flask containing 300 cc methyl alcohol and 8 a magnesium carbonate. 10 l/h CO and 10 l/h C_2H_2 are then passed through the flask. The temperature is kept at 40° C. by means of a water bath. The addition of the reactants requires 4 hours. The reaction is continued for 5 hours in total. 10 g nickel

carbonyl are consumed. 21 g raw product are obtained, from which, by vacuum distillation, 14 g of a fraction passing at 120—130° C/6 mm Hg and containing 7-acetoxy-2,5-heptadienoic methyl ester, are obtained.

EXAMPLE 17.

10 g raw 1.8-dichloro-2,6-octadiene are reacted with 10 g nickel carbonyl for 4 hours at 35° C. under CO and C_2H_2 in 200 cc methyl alcohol.

By distillation at 200—210° C/10 mm Hg, about 3 g tetradeca-2,5,9,12-tetraendoic acid dimethyl ester, are obtained.

This product by hydrogenation on Pd at room temperature yields a white solid product melting at 41° C and consisting of tetradecandioic dimethyl ester.

EXAMPLE 18.

Into a small 1 litre glass reaction column with a diameter of 50 mm. 500 cc methanol are introduced and a gaseous mixture containing 65% acetylene and 35% carbon monoxide is circulated at 40° C in the same apparatus. A 10 litres reservoir is inserted in the cycle.

A solution of 200 cc chlorocyanobutene in 500 cc methanol and a solution of 45 cc nickel carbonyl in 500 cc methanol are then added over 7 hours. After 45 minutes the absorption is so high that the addition of further acetylene and carbon monoxide is required which can be regulated in order to maintain the acetylene proportion at about 60%. The temperature is kept constant by circulating air in the jacket. The liquid which fills the reaction column flows out through an overflow and is collected in a suitable collector. When the reaction is completed nitrogen is introduced and the product is discharged.

The total consumption of nickel carbonyl, found as nickel chloride, corresponds to 20 g. Methyl alcohol is distilled off and nickel chloride is separated as an aqueous solution; the product obtained is vacuum distilled thus obtaining the following fractions: 9 g distillation heads up to 140°/10 mm Hg, 184 g product distilled at 140—168° C/14 mm Hg, containing 135 g methyl ester 7-cyano-2,5-heptadienoic acid together with 2,5-octadienoic diester, and 11 g residue distilling up to 178°/14 mm Hg.

EXAMPLE 19.

300 cc methyl alcohol are placed in the reaction column of the preceding example. A mixture of 65% C_2H_2 and 35% CO is then circulated at a flow rate of about 100 litres/h. Two solutions of 100 cc methanol, one containing 20 g chlorocyanobutene and the other 3 cc nickel carbonyl are then introduced within 3 hours. After 45 minutes the solution becomes darker until it assumes a brown-red colour. Further CO and C_2H_2 are introduced maintaining the pressure of the cycle at 20 cm H_2O at the circulation pump and the acetylene proportion at about 65%. Temperature is kept at 40° C. When the reaction is completed the solution is discoloured. The solution is discharged from the bottom of the column and the operation is repeated with the same amounts of reactants. The whole product is transferred to a flask from which methanol is distilled off. Water is added and the nickel chloride solution is separated. The product collected in ethyl ether and dried on sodium sulphate is then distilled. After 2.2 g distillation heads containing unreacted chlorocyanobutene, 49 g distillate containing 7-cyano-2,5-heptadienoic methyl ester are obtained at 140—155° C/11 mm Hg. The amount of nickel present in the aqueous solution as nickel chloride is 2.07 g.

EXAMPLE 20.

300 cc acetone and 300 cc water are introduced into the reaction tube and CO and C_2H_2 are passed through as in the preceding example. Two acetone solutions, one containing 40 g chloro-cyanobutene and the other 7 cc nickel carbonyl, are then introduced. Finally, the gas is discharged and the apparatus is washed with nitrogen. The reaction is carried out as in the preceding example. When the reaction is completed acetone is distilled off, the product is separated from nickel chloride and treated with sodium carbonate thus extracting the acid portion which is then freed by acidification with sulphuric acid and is mixed with ether. The acid portion, containing 7-cyano-2,5-heptadienoic acid amounts to 34 g. (The acidimetric equivalent is 165).

EXAMPLE 21.

300 cc methanol are mixed with 30 g hydrated nickel acetate under the conditions of Example 19 the mixture is reacted with CO, C_2H_2, $Ni(CO)_4$(6 cc) and chlorocyanobutene (40 g). 37 g of a distillate at between 140 and 160° C (10 mm Hg) are obtained. The absorbed carbon monoxide corresponds to 5.14 litres. The nickel amount found in the solution and exceeding the starting nickel amount is 1 g.

EXAMPLE 22.

25 g allyl chloride in 200 cc methanol solution and 13 cc nickel carbonyl in 100 cc methanol solution are introduced over 3 hours into the reaction tube which contains 300 cc methanol, under a stream of acetylene and carbon monoxide. Temperature is kept at 40° C. After 3 hours reaction the gas is discharged and the reaction mixture is washed with nitrogen.

The solution obtained is distilled up to 80° C and the residue obtained is collected in ether. From the distilled methanol further

product is obtained by treatment with a saturated calcium chloride solution. By vacuum distillation of the product of two runs, 28 g methyl 2,5-hexadienoate, with a boiling point of 63—66° C, (34 mm Hg), are obtained. 8 g nickel are found in the solution as chloride.

EXAMPLE 23.

80 g allyl chloride diluted with 1200 cc methanol together with 36 cc nickel carbonyl in 400 cc methanol are continuously introduced into a reactor at 40—45° for 8 hours. The circulation of CO and C_2H_2 amounts to about 100 litres per hour. By distilling the product and treating the alcohol with a calcium chloride solution, 50 g are recovered, consisting of methyl-2,5-hexadienoate. 17 g nickel are found in the solution as chloride.

EXAMPLE 24.

Two solutions of 20 g crotyl chloride and 9 cc nickel carbonyl, each in 100 cc methanol, are introduced into a reaction tube, containing 200 cc methanol, in which CO and C_2H_2 are circulated as in the preceding examples.

The temperature during the reaction is kept at 30° C. The reaction time is 3 hours. By distilling the reaction liquid, 13 g methyl 2,5-heptadienoate with a boiling point of 72—75° (20 mm Hg) are obtained.

3.2 g nickel are consumed.

WHAT WE CLAIM IS:—

1. α-β,δ-ε-unsaturated carboxylic derivatives having the general formula:—

$$R—[(CH_2)_{n^1}—CH=CH—CH_2—CH=CH—COOR^1]_n$$

where n is 1 or 2.

n^1 is 0 or 1.

R is H or an aliphatic group containing up to 20 carbon atoms with or without substituent groups, and

R^1 is H or an aliphatic, hydroxyaliphatic or aryl-aliphatic or cycloaliphatic group containing not more than 20 carbon atoms, except 2,5-heptadienoic acid and 2,5-octadienoic acids in which the double bond conjugated with the carboxyl group is in the trans-configuration.

2. 2,5-hexadienoic acid.

3. Methyl ester of 2,5-hexadienoic acid.

4. Ethyl ester of 2,5-hexadienoic acid.

5. Isopropyl ester of 2,5-hexadienoic acid.

6. Benzyl ester of 2,5-hexadienoic acid.

7. Ethylene glycol esters of 2,5-hexadienoic acid.

8. 2,5-heptadienoic acid in which the double bond which is conjugated with the carboxyl group is in the *cis*-configuration.

9. Methyl ester of 2,5-heptadienoic acid.

10. Methyl 7-acetoxy-2,5-heptadienoate.

11. 7-cyano-2,5-heptadienoic acid.

12. Methyl ester of 7-cyano-2,5-heptadienoic acid.

13. Isopropyl ester of 7-cyano-2,5-heptadienoic acid.

14. Cyclohexyl ester of 7-cyano-2,5-heptadienoic acid.

15. Dimethyl ester of 2,5-octadiendioic acid.

16. Dimethyl tetradeca-2,5,9,12-tetraendioate.

17. A method for the preparation of α-β,δ-ε-unsaturated carboxylic derivatives having the general formula defined in Claim 1, which comprises reacting an allyl derivative of the general formula

$$R—((CH_2)_{n^1}—CH=CH—CH_2Cl)_n$$

wherein R, n^1, and n are as defined in Claim 1 and acetylene with a solution of nickel carbonyl in a solvent having the general formula R^1OH wherein R^1 is as defined in Claim 1.

18. A method according to Claim 17, in which the acetylene is admixed with carbon monoxide.

19. A method according to Claim 17 or 18 in which an excess of acetylene over the allyl derivatives is employed.

20. A method according to Claim 19 in which said excess is at least 20%.

21. A method according to any one of Claims 17 to 20 in which an excess of nickel carbonyl is employed.

22. A method according to any one of Claims 17 to 21, in which the reaction is carried out at a temperature of from 0 to 75° C. and at atmospheric pressure.

23. A method according to Claim 22, in which the temperature is from 25 to 60° C.

24. A method according to any one of Claims 17 to 23 in which the allyl derivative is prepared by chlorination of the corresponding olefin.

25. A method according to any one of Claims 17 to 24 in which buffers are employed to neutralize the free hydrochloric acid.

26. A method according to Claim 25 in which magnesium carbonate, calcium carbonate or sodium dihydrogen phosphate is employed as buffer.

27. A method according to any one of Claims 17 to 24 in which an inert solvent is used.

28. A method according to Claim 27 in which acetone, a glycol ether or diethyl ketone is employed as solvent.

29. A method for the preparation of the compounds defined in Claim 1, substantially as hereinbefore described with reference to the foregoing examples.

30. Compounds of the general formula defined in Claim 1 when prepared by the method claimed in any one of Claims 17 to 29.

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